General

Guideline Title

Sepsis: recognition, diagnosis and early management.

Bibliographic Source(s)

National Guideline Centre. Sepsis: recognition, diagnosis and early management. London (UK): National Institute for Health and Care Excellence (NICE); 2016 Jul 13. 50 p. (NICE guideline; no. 51).

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Note from the National Guideline Clearinghouse (NGC): The guideline was developed by the National Guideline Centre on behalf of the National Institute for Health and Care Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance and related appendices.

The wording used in the recommendations in this guideline (for example, words such as 'offer' and 'consider') denotes the certainty with which the recommendation is made (the strength of the recommendation) and is defined at the end of the "Major Recommendations" field.

Identifying People with Suspected Sepsis

This guidance should be used together with the algorithms organised by age group and treatment location and the risk stratification tools in the original guideline document (see the "Clinical Algorithm[s]" field).

Think 'could this be sepsis?' if a person presents with signs or symptoms that indicate possible infection.

Take into account that people with sepsis may have non-specific, non-localised presentations, for example, feeling very unwell, and may not have a high temperature.

Pay particular attention to concerns expressed by the person and their family or carers, for example, changes from usual behaviour.

Assess people who might have sepsis with extra care if they cannot give a good history (for example, people with English as a second language or people with communication problems).

Assess people with any suspected infection to identify:

- Possible source of infection
- Factors that increase risk of sepsis (see "Risk Factors for Sepsis," below)
- Any indications of clinical concern, such as new onset abnormalities of behaviour, circulation or respiration

Identify factors that increase risk of sepsis (see "Risk Factors for Sepsis," below) or indications of clinical concern such as new onset abnormalities of behaviour, circulation or respiration when deciding during a remote assessment whether to offer a face-to-face-assessment and if so, on the urgency of face-to-face assessment.

Use a structured set of observations (see "Face-to-face Assessment of People with Suspected Sepsis," below) to assess people in a face-to-face setting to stratify risk (see "Stratifying Risk of Severe Illness or Death from Sepsis," below) if sepsis is suspected.

Consider using an early warning score to assess people with suspected sepsis in acute hospital settings.

Suspect neutropenic sepsis in patients having anticancer treatment who become unwell. (This recommendation is from NICE's guideline on neutropenic sepsis [see the NGC summary of the NICE guideline Neutropenic sepsis: prevention and management of neutropenic sepsis in cancer patients].)

Refer patients with suspected neutropenic sepsis immediately for assessment in secondary or tertiary care. (This recommendation is from NICE's guideline on neutropenic sepsis [see the NGC summary of the NICE guideline Neutropenic sepsis: prevention and management of neutropenic sepsis in cancer patients].)

Treat people with neutropenic sepsis in line with NICE's guideline on neutropenic sepsis (see the NGC summary of the NICE guideline Neutropenic sepsis: prevention and management of neutropenic sepsis in cancer patients).

Risk Factors for Sepsis

Take into account that people in the groups below are at higher risk of developing sepsis:

- The very young (under 1 year) and older people (over 75 years) or people who are very frail
- People who have impaired immune systems because of illness or drugs, including:
  - People being treated for cancer with chemotherapy (see "Identifying People with Suspected Sepsis," above)
  - People who have impaired immune function (for example, people with diabetes, people who have had a splenectomy, or people with sickle cell disease)
  - People taking long-term steroids
  - People taking immunosuppressant drugs to treat non-malignant disorders such as rheumatoid arthritis
- People who have had surgery, or other invasive procedures, in the past 6 weeks
- People with any breach of skin integrity (for example, cuts, burns, blisters or skin infections)
- People who misuse drugs intravenously
- People with indwelling lines or catheters

Take into account that women who are pregnant, have given birth or had a termination of pregnancy or miscarriage in the past 6 weeks are in a high risk group for sepsis. In particular, women who:

- Have impaired immune systems because of illness or drugs (see "Identifying People with Suspected Sepsis," above)
- Have gestational diabetes or diabetes or other comorbidities
- Needed invasive procedures (for example, caesarean section, forceps delivery, removal of retained products of conception)
- Had prolonged rupture of membranes
- Have or have been in close contact with people with group A streptococcal infection, for example, scarlet fever
- Have continued vaginal bleeding or an offensive vaginal discharge

Take into account the following risk factors for early-onset neonatal infection:

- Invasive group B streptococcal infection in a previous baby
- Maternal group B streptococcal colonisation, bacteriuria or infection in the current pregnancy
- Prelabour rupture of membranes
- Preterm birth following spontaneous labour (before 37 weeks' gestation)
- Suspected or confirmed rupture of membranes for more than 18 hours in a preterm birth

- Intrapartum fever higher than 38°C, or confirmed or suspected chorioamnionitis
- Parenteral antibiotic treatment given to the woman for confirmed or suspected invasive bacterial infection (such as septicaemia) at any time during labour, or in the 24-hour periods before and after the birth (this does not refer to intrapartum antibiotic prophylaxis)
- Suspected or confirmed infection in another baby in the case of a multiple pregnancy

(This recommendation is from NICE's guideline on neonatal infection [see the NGC summary of the NICE guideline Antibiotics for early-onset neonatal infection. Antibiotics for the prevention and treatment of early-onset neonatal infection].)

Face-to-face Assessment of People with Suspected Sepsis

Assess temperature, heart rate, respiratory rate, blood pressure, level of consciousness and oxygen saturation in young people and adults with suspected sepsis.

Assess temperature, heart rate, respiratory rate, level of consciousness, oxygen saturation and capillary refill time in children under 12 years with suspected sepsis. (This recommendation is adapted from NICE's guideline on fever in under 5s [see the NGC summary of the NICE guideline Feverish illness in children: assessment and initial management in children younger than 5 years].)

Measure blood pressure of children under 5 years if heart rate or capillary refill time is abnormal and facilities to measure blood pressure, including a correctly-sized blood pressure cuff, are available. (This recommendation is adapted from NICE's guideline on fever in under 5s [see the NGC summary of the NICE guideline Feverish illness in children: assessment and initial management in children younger than 5 years].)

Measure blood pressure of children aged 5 to 11 years who might have sepsis if facilities to measure blood pressure, including a correctly-sized cuff, are available.

Only measure blood pressure in children under 12 years in community settings if facilities to measure blood pressure, including a correctly-sized cuff, are available and taking a measurement does not cause a delay in assessment or treatment.

Measure oxygen saturation in community settings if equipment is available and taking a measurement does not cause a delay in assessment or treatment.

Examine people with suspected sepsis for mottled or ashen appearance, cyanosis of the skin, lips or tongue, non-blanching rash of the skin, any breach of skin integrity (for example, cuts, burns or skin infections) or other rash indicating potential infection.

Ask the person, parent or carer about frequency of urination in the past 18 hours.

Stratifying Risk of Severe Illness or Death from Sepsis

Use the person's history and physical examination results to grade risk of severe illness or death from sepsis using criteria based on age (see Tables 1, 2, and 3 in the original guideline document).

Adults, Children and Young People Aged 12 Years and Over

Table 1 in the original guideline document demonstrates risk stratification tool for adults, children and young people aged 12 years and over with suspected sepsis (a downloadable version of this table is also available).

Recognise that adults, children and young people aged 12 years and over with suspected sepsis and any of the symptoms or signs below are at high risk of severe illness or death from sepsis:

- Objective evidence of new altered mental state
- Respiratory rate of 25 breaths per minute or above, or new need for 40% oxygen or more to maintain oxygen saturation more than 92% (or more than 88% in known chronic obstructive pulmonary disease)
- Heart rate of 130 beats per minute or above
- Systolic blood pressure of 90 mmHg or less, or systolic blood pressure more than 40 mmHg below normal
- Not passed urine in previous 18 hours (for catheterised patients, passed less than 0.5 ml/kg/hour)
- Mottled or ashen appearance
- Cyanosis of the skin, lips or tongue
- Non-blanching rash of the skin

Recognise that adults, children and young people aged 12 years and over with suspected sepsis and any of the symptoms or signs below are at moderate to high risk of severe illness or death from sepsis:

- History of new-onset changed behaviour or change in mental state, as reported by the person, a friend or relative
- History of acute deterioration of functional ability
- Impaired immune system (illness or drugs, including oral steroids)
- Trauma, surgery or invasive procedure in the past 6 weeks
- Respiratory rate of 21 to 24 breaths per minute, heart rate of 91 to 130 beats per minute or new-onset arrhythmia or if pregnant, heart rate of 100 to 130 beats per minute
- Systolic blood pressure of 91 to 100 mmHg
- Not passed urine in the past 12 to 18 hours (for catheterised patients, passed 0.5–1 ml/kg/hour)
- Tympanic temperature less than 36°C
- Signs of potential infection, including increased redness, swelling or discharge at a surgical site, or breakdown of a wound

Consider adults, children and young people aged 12 years and over with suspected sepsis who do not meet any high or moderate to high risk criteria to be at low risk of severe illness or death from sepsis.

Children Aged 5 to 11 Years

Table 2 in the original guideline document shows risk stratification tool for children aged 5 to 11 years with suspected sepsis (a downloadable version of this table is also available).

Recognise that children aged 5 to 11 years with suspected sepsis and any of the symptoms or signs below are at high risk of severe illness or death from sepsis:

- Has objective evidence of altered behaviour or mental state, or appears ill to a healthcare professional, or does not wake (or if roused, does not stay awake)
- Respiratory rate:
  - Aged 5 years, 29 breaths per minute or more
  - Aged 6 to 7 years, 27 breaths per minute or more
  - Aged 8 to 11 years, 25 breaths per minute or more
  - Oxygen saturation of less than 90% in air or increased oxygen requirement over baseline
- Heart rate:
  - Aged 5 years, 130 beats per minute or more
  - Aged 6 to 7 years, 120 beats per minute or more
  - Aged 8 to 11 years, 115 beats per minute or more
  - Or heart rate less than 60 beats per minute at any age
- Mottled or ashen appearance
- Cyanosis of the skin, lips or tongue
- Non-blanching rash of the skin

Recognise that children aged 5 to 11 years with suspected sepsis and any of the symptoms or signs below are at moderate to high risk of severe illness or death from sepsis:

- Not responding normally to social cues or decreased activity, or parent or carer concern that the child is behaving differently from usual
- Respiratory rate:
  - Aged 5 years, 24 to 28 breaths per minute
  - Aged 6 to 7 years, 24 to 27 breaths per minute
  - Aged 8 to 11 years, 22 to 24 breaths per minute
  - Oxygen saturation of less than 92% in air or increased oxygen requirement over baseline
- Heart rate:
  - Aged 5 years, 120 to 129 beats per minute
  - Aged 6 to 7 years, 110 to 119 beats per minute
  - Aged 8 to 11 years, 105 to 114 beats per minute
  - Or capillary refill time of 3 seconds or more
- Reduced urine output, or for catheterised patients passed less than 1 ml/kg of urine per hour
- Have leg pain or cold hands and feet

Consider children aged 5 to 11 years with suspected sepsis who do not meet any high or moderate to high risk criteria to be at low risk of severe illness or death from sepsis.

Children Aged under 5 Years

Table 3 in the original guideline document shows risk stratification tool for children aged under 5 years with suspected sepsis. This table is adapted from NICE's guideline on fever in under 5s (see the NGC summary of the NICE guideline Feverish illness in children: assessment and initial management in children younger than 5 years). A downloadable version of this table is also available.

Recognise that children aged under 5 years with suspected sepsis and any of the symptoms or signs below are at high risk of severe illness or death from sepsis:

- Behaviour:
  - No response to social cues
  - Appears ill to a healthcare professional
  - Does not wake, or if roused does not stay awake
  - Weak, high-pitched or continuous cry
- Heart rate:
  - Aged under 1 year, 160 beats per minute or more
  - Aged 1 to 2 years, 150 beats per minute or more
  - Aged 3 to 4 years, 140 beats per minute or more
  - Heart rate less than 60 beats per minute at any age
- Respiratory rate:
  - Aged under 1 year, 60 breaths per minute or more
  - Aged 1 to 2 years, 50 breaths per minute or more
  - Aged 3 to 4 years, 40 breaths per minute or more
  - Grunting
  - Apnoea
  - Oxygen saturation of less than 90% in air or increased oxygen requirement over baseline
- Mottled or ashen appearance
- Cyanosis of the skin, lips or tongue
- Non-blanching rash of the skin
- Aged under 3 months and temperature 38°C or more
- Temperature less than 36°C

(This recommendation is adapted from NICE's guideline on fever in under 5s [see the NGC summary of the NICE guideline Feverish illness in children: assessment and initial management in children younger than 5 years].)

Recognise that children aged under 5 years with suspected sepsis and any of the symptoms or signs below are at moderate to high risk of severe illness or death from sepsis:

- Behaviour:
  - No response to social cues
  - No smile
  - Wakes only with prolonged stimulation
  - Decreased activity
  - Parent or carer concern that the child is behaving differently from usual
- Respiratory rate:
  - Aged under 1 year, 50 to 59 breaths per minute
  - Aged 1 to 2 years, 40 to 49 breaths per minute
  - Aged 3 to 4 years, 35 to 39 breaths per minute
  - Oxygen saturation 91% or less in air or increased oxygen requirement over baseline
  - Nasal flaring
- Heart rate:
  - Aged under 1 year, 150 to 159 beats per minute
  - Aged 1 to 2 years, 140 to 149 beats per minute
  - Aged 3 to 4 years, 130 to 139 beats per minute
- Capillary refill time of 3 seconds or more
- Reduced urine output, or for catheterised patients passed less than 1 ml/kg of urine per hour

- Is pale or flushed or has pallor of skin, lips or tongue reported by parent or carer
- Aged 3 to 6 months and temperature 39°C or over
- Have leg pain or cold hands or feet

(This recommendation is adapted from NICE's guideline on fever in under 5s [see the NGC summary of the NICE guideline Feverish illness in children: assessment and initial management in children younger than 5 years].)

Consider children aged under 5 years with suspected sepsis who do not meet any high or moderate to high risk criteria to be at low risk of severe illness or death from sepsis. (This recommendation is adapted from NICE's guideline on fever in under 5s [see the NGC summary of the NICE guideline Feverish illness in children: assessment and initial management in children younger than 5 years].)

Children, Young People and Adults with Suspected Sepsis

Temperature in Suspected Sepsis

Do not use a person's temperature as the sole predictor of sepsis.

Do not rely on fever or hypothermia to rule sepsis either in or out.

Ask the person with suspected sepsis and their family or carers about any recent fever or rigors.

Take into account that some groups of people with sepsis may not develop a raised temperature. These include:

- People who are older or very frail
- People having treatment for cancer
- People severely ill with sepsis
- Young infants or children

Take into account that a rise in temperature can be a physiological response, for example after surgery or trauma.

Heart Rate in Suspected Sepsis

Interpret the heart rate of a person with suspected sepsis in context, taking into account that:

- Baseline heart rate may be lower in young people and adults who are fit
- Baseline heart rate in pregnancy is 10 to 15 beats per minute more than normal
- Older people with an infection may not develop an increased heart rate
- Older people may develop a new arrhythmia in response to infection rather than an increased heart rate
- Heart rate response may be affected by medicines such as beta-blockers

Blood Pressure in Suspected Sepsis

Interpret blood pressure in the context of a person's previous blood pressure, if known. Be aware that the presence of normal blood pressure does not exclude sepsis in children and young people.

Confusion, Mental State and Cognitive State in Suspected Sepsis

Interpret a person's mental state in the context of their normal function and treat changes as being significant.

Be aware that changes in cognitive function may be subtle and assessment should include history from patient and family or carers.

Take into account that changes in cognitive function may present as changes in behaviour or irritability in both children and in adults with dementia.

Take into account that changes in cognitive function in older people may present as acute changes in functional abilities.

Oxygen Saturation in Suspected Sepsis

Take into account that if peripheral oxygen saturation is difficult to measure in a person with suspected sepsis, this may indicate poor peripheral circulation because of shock.

Managing Suspected Sepsis Outside Acute Hospital Settings

Refer all people with suspected sepsis outside acute hospital settings for emergency medical care[1] by the most appropriate means of transport

(usually 999 ambulance) if:

- They meet any high risk criteria (see Tables 1, 2, and 3 in the original guideline document) or
- They are aged under 17 years and their immunity is impaired by drugs or illness and they have any moderate to high risk criteria

Assess all people with suspected sepsis outside acute hospital settings with any moderate to high risk criteria to:

- Make a definitive diagnosis of their condition
- Decide whether they can be treated safely outside hospital

If a definitive diagnosis is not reached or the person cannot be treated safely outside an acute hospital setting, refer them urgently for emergency care.

Provide people with suspected sepsis, who do not have any high or moderate to high risk criteria information about symptoms to monitor and how to access medical care if they are concerned.

Managing and Treating Suspected Sepsis in Acute Hospital Settings

Adults, Children and Young People Aged 12 Years and Over with Suspected Sepsis Who Meet 1 or More High Risk Criteria

For adults, children and young people aged 12 years and over who have suspected sepsis and 1 or more high risk criteria:

- Arrange for immediate review by the senior clinical decision maker[2] to assess the person and think about alternative diagnoses to sepsis
- Carry out a venous blood test for the following:
  - Blood gas, including glucose and lactate measurement
  - Blood culture
  - Full blood count
  - C-reactive protein
  - Urea and electrolytes
  - Creatinine
  - A clotting screen
- Give a broad-spectrum antimicrobial at the maximum recommended dose without delay (within 1 hour of identifying that they meet any high risk criteria in an acute hospital setting) in line with recommendations in the "Antibiotic Treatment in People with Suspected Sepsis" section below.
- Discuss with a consultant[3]

For adults, children and young people aged 12 years and over with suspected sepsis and any high risk criteria and lactate over 4 mmol/litre, or systolic blood pressure less than 90 mmHg:

- Give intravenous fluid bolus without delay (within 1 hour of identifying that they meet any high risk criteria in an acute hospital setting) in line with recommendations in the "Intravenous Fluids in People with Suspected Sepsis" section and
- Refer[4] to critical care[5] for review of management including need for central venous access and initiation of inotropes or vasopressors

For adults, children and young people aged 12 years and over with suspected sepsis and any high risk criteria and lactate between 2 and 4 mmol/litre:

- Give intravenous fluid bolus without delay (within 1 hour of identifying that they meet any high risk criteria in an acute hospital setting) in line with recommendations in the "Intravenous Fluids in People with Suspected Sepsis" section

For adults, children and young people aged 12 years and over with suspected sepsis and any high risk criteria and lactate below 2 mmol/litre:

- Consider giving intravenous fluid bolus (in line with recommendations in "Intravenous Fluids in People with Suspected Sepsis" section)

Monitor people with suspected sepsis who meet any high risk criteria continuously, or a minimum of once every 30 minutes depending on setting. Physiological track and trigger systems should be used to monitor all adult patients in acute hospital settings. (This recommendation is adapted from NICE's guideline on acutely ill patients in hospital .)

Monitor the mental state of adults, children and young people aged 12 years and over with suspected sepsis. Consider using a scale such as the Glasgow Coma Scale (GCS) or ('alert, voice, pain, unresponsive') scale.

Alert a consultant to attend in person if an adult, child or young person aged 12 years or over with suspected sepsis and any high risk criteria fails to respond within 1 hour of initial antibiotic and/or intravenous fluid resuscitation. Failure to respond is indicated by any of:

- Systolic blood pressure persistently below 90 mmHg
- Reduced level of consciousness despite resuscitation
- Respiratory rate over 25 breaths per minute or a new need for mechanical ventilation
- Lactate not reduced by more than 20% of initial value within 1 hour

Adults, Children and Young People Aged 12 Years and Over with Suspected Sepsis Who Meet 2 or More Moderate to High Risk Criteria

For adults, children and young people aged 12 years and over with suspected sepsis and 2 or more moderate to high risk criteria, or systolic blood pressure 91 to 100 mmHg, carry out a venous blood test for the following:

- Blood gas, including glucose and lactate measurement
- Blood culture
- Full blood count
- C-reactive protein
- Urea and electrolytes
- Creatinine

  and arrange for a clinician[6] to review the person's condition and venous lactate results within 1 hour of meeting criteria in an acute hospital setting.

For adults, children and young people aged 12 years and over with suspected sepsis who meet 2 or more moderate to high risk criteria and have lactate over 2 mmol/litre or evidence of acute kidney injury[7], treat as high risk and follow recommendations in the "Adults, Children and Young People Aged 12 Years and Over with Suspected Sepsis Who Meet 1 or More High Risk Criteria" section above.

For adults, children and young people aged 12 years and over with suspected sepsis who meet 2 or more moderate to high risk criteria, have lactate of less than 2 mmol/litre, no evidence of acute kidney injury[7] and in whom a definitive condition cannot be identified:

- Repeat structured assessment at least hourly
- Ensure review by a senior clinical decision maker[2] within 3 hours of meeting 2 or more moderate to high risk criteria in an acute hospital setting for consideration of antibiotics

For adults, children and young people aged 12 years and over with suspected sepsis who meet 2 or more moderate to high risk criteria, have lactate of less than 2 mmol/litre, no evidence of acute kidney injury[7] and in whom a definitive condition or infection can be identified and treated:

manage the definitive condition
if appropriate, discharge with information depending on the setting (see recommendations under "," below)

Adults, Children and Young People Aged 12 Years and Over with Suspected Sepsis Who Meet Only 1 Moderate to High Risk Criterion

For adults, children and young people aged 12 years and over with suspected sepsis who meet only 1 moderate to high risk criterion:

- Arrange clinician[6] review within 1 hour of meeting criterion for clinical assessment in an acute hospital setting
- Perform blood tests if indicated

For adults, children and young people aged 12 years and over with suspected sepsis who meet only 1 moderate to high risk criterion and in whom a definitive condition can be identified and treated:

- Manage the definitive condition
- If appropriate, discharge with information depending on setting (see recommendations under "Information at Discharge for People Assessed for Suspected Sepsis, But Not Diagnosed with Sepsis" below)

For adults, children and young people aged 12 years and over with suspected sepsis who meet only 1 moderate to high risk criterion, have lactate of less than 2 mmol/litre, no evidence of acute kidney injury[7] and in whom a definitive condition cannot be identified:

- Repeat structured assessment at least hourly.
- Ensure review by a senior clinical decision maker[2] within 3 hours of meeting moderate to high criterion in an acute hospital setting for

consideration of antibiotics

Adults, Children and Young People Aged 12 Years and Over with Suspected Sepsis and No High Risk or Moderate to High Risk Criteria

Arrange clinical assessment[8] of adults, children and young people aged 12 years and over who have suspected sepsis and no high risk or moderate to high risk criteria and manage according to clinical judgement.

Children Aged 5 to 11 Years

Children Aged 5 to 11 Years with Suspected Sepsis Who Meet 1 or More High Risk Criteria

For children aged 5 to 11 years who have suspected sepsis and 1 or more high risk criteria:

- Arrange for immediate review by the senior clinical decision maker[9] to assess the child and think about alternative diagnoses to sepsis
- Carry out a venous blood test for the following:
  - Blood gas, including glucose and lactate measurement
  - Blood culture
  - Full blood count
  - C-reactive protein
  - Urea and electrolytes
  - Creatinine
  - A clotting screen
- Give a broad-spectrum antimicrobial (see "Antibiotic Treatment in People with Suspected Sepsis," below) at the maximum recommended dose without delay (within 1 hour of identifying that they meet any high risk criteria in an acute hospital setting)
- Discuss with a consultant

For children aged 5 to 11 years with suspected sepsis and any high risk criteria and lactate over 4 mmol/litre:

- Give intravenous fluid bolus without delay (within 1 hour of identifying that they meet any high risk criteria in an acute hospital setting) in line with recommendations under "Intravenous Fluids in People with Suspected Sepsis," below and
- Refer[4] to critical care[5] for review of central access and initiation of inotropes or vasopressors

For children aged 5 to 11 years with suspected sepsis and any high risk criteria and lactate between 2 and 4 mmol/litre:

- Give intravenous fluid bolus as soon as possible (within 1 hour of identifying that they meet any high risk criteria in an acute hospital setting) in line with recommendations in "Intravenous Fluids in People with Suspected Sepsis"

For children aged 5 to 11 years with suspected sepsis and any high risk criteria and lactate below 2 mmol/litre:

- Consider giving intravenous fluid bolus in line with recommendations under "Intravenous Fluids in People with Suspected Sepsis," below

Monitor children with suspected sepsis who meet any high risk criteria continuously, or a minimum of once every 30 minutes depending on setting. Physiological track and trigger systems should be used to monitor all children in acute hospital settings. (This recommendation is adapted from NICE's guideline on acutely ill patients in hospital .)

Monitor the mental state of children aged 5 to 11 years with suspected sepsis. Consider using the GCS or AVPU scale.

Alert a consultant to attend in person if a child aged 5 to 11 years with suspected sepsis and any high risk criteria fails to respond within 1 hour of initial antibiotic and/or intravenous fluid resuscitation. Failure to respond is indicated by any of:

- Reduced level of consciousness despite resuscitation
- Heart rate or respiratory rate fulfil high risk criteria
- Lactate remains over 2 mmol/litre after 1 hour

Children Aged 5 to 11 Years with Suspected Sepsis Who Meet 2 or More Moderate to High Risk Criteria

For children aged 5 to 11 years who have suspected sepsis and 2 or more moderate to high risk criteria:

- Carry out a venous blood test for the following:
  - Blood gas, including glucose and lactate measurement

    - Blood culture
    - Full blood count
    - C-reactive protein
    - Urea and electrolytes
    - Creatinine
- Arrange for a clinician to review the person's condition and venous lactate results within 1 hour of meeting criteria in an acute hospital setting

For children aged 5 to 11 years with suspected sepsis who meet 2 or more moderate to high risk criteria and have lactate over 2 mmol/litre, treat as high risk and follow recommendations under "Children Aged 5 to 11 Years with Suspected Sepsis Who Meet 1 or More High Risk Criteria," above.

For children aged 5 to 11 years with suspected sepsis who meet 2 or more moderate to high risk criteria, have lactate of less than 2 mmol/litre, and in whom a definitive condition cannot be identified:

- Repeat structured assessment at least hourly
- Ensure review by a senior clinical decision maker[9] within 3 hours of meeting 2 or more moderate to high risk criteria in an acute hospital setting for consideration of antibiotics

For children aged 5 to 11 years with suspected sepsis who meet 2 or more moderate to high risk criteria, have lactate of less than 2 mmol/litre, and in whom a definitive condition or infection can be identified and treated:

- Manage the definitive condition, and
- If appropriate, discharge with information depending on setting (see recommendations under "Information at Discharge for People Assessed for Suspected Sepsis, But Not Diagnosed with Sepsis," below)

Children Aged 5 to 11 Years with Suspected Sepsis Who Meet Only 1 Moderate to High Risk Criterion

For children aged 5 to 11 years with suspected sepsis who meet only 1 moderate to high risk criterion:

- Arrange clinician[6] review within 1 hour of meeting 1 moderate to high risk criterion in an acute hospital setting for clinical assessment and
- Perform blood tests if indicated

For children aged 5 to 11 years with suspected sepsis who meet only 1 moderate to high risk criterion and in whom a definitive condition can be identified and treated:

- Manage the definitive condition
- If appropriate, discharge with information depending on setting (see "Information at Discharge for People Assessed for Suspected Sepsis, But Not Diagnosed with Sepsis," below)

For children aged 5 to 11 years with suspected sepsis who meet only 1 moderate to high risk criterion, and in whom a definitive condition cannot be identified:

- Repeat structured assessment at least hourly
- Ensure review by a senior clinical decision maker[9] within 3 hours of meeting a moderate to high risk criterion in an acute hospital setting for consideration of antibiotics

Children Aged 5 to 11 Years with Suspected Sepsis and No High Risk or Moderate to High Risk Criteria

Arrange clinical assessment[10] of children aged 5 to 11 years who have suspected sepsis and no high risk or moderate to high risk criteria and manage according to clinical judgement.

Children Aged Under 5 Years

Children Aged under 5 Years with Suspected Sepsis Who Meet 1 or More High Risk Criteria

For children aged under 5 years who have suspected sepsis and 1 or more high risk criteria:

- Arrange for immediate review by the senior clinical decision maker[11] to assess the child and think about alternative diagnoses to sepsis (for example bronchiolitis)

- Carry out a venous blood test for the following:
  - Blood gas, including glucose and lactate measurement
  - Blood culture
  - Full blood count
  - C-reactive protein
  - Urea and electrolytes
  - Creatinine
  - A clotting screen
- Give a broad-spectrum antimicrobial at the maximum recommended dose without delay (within 1 hour of identifying that they meet any high risk criteria in an acute hospital setting; see "Antibiotic Treatment in People with Suspected Sepsis," below)
- Discuss with a consultant

For children aged under 5 years with suspected sepsis and any high risk criteria and lactate over 4 mmol/litre:

- Give intravenous fluid bolus without delay (in line with recommendations under "Intravenous Fluids in People with Suspected Sepsis," below), and
- Refer[4] to critical care[5] for review of central access and initiation of inotropes or vasopressors

For children aged under 5 years with suspected sepsis and any high risk criteria and lactate between 2 and 4 mmol/litre:

- Give intravenous fluid bolus without delay (within 1 hour of identifying that they meet any high risk criteria in an acute hospital setting) in line with recommendations under "Intravenous Fluids in People with Suspected Sepsis," below.

For children aged under 5 years with suspected sepsis and any high risk criteria and lactate below 2 mmol/litre, consider giving intravenous fluid bolus in line with recommendations under "Intravenous Fluids in People with Suspected Sepsis," below.

Monitor children aged under 5 years with suspected sepsis who meet any high risk criteria continuously, or a minimum of once every 30 minutes depending on setting. Physiological track and trigger systems should be used to monitor all children in acute hospital settings. (This recommendation is adapted from NICE's guideline on acutely ill patients in hospital .)

Monitor the mental state of children under 5 years with suspected sepsis. Consider using the GCS or AVPU scale.

Alert a consultant to attend in person if a child aged under 5 years with suspected sepsis and any high risk criteria fails to respond within 1 hour of initial antibiotic and/or intravenous fluid resuscitation. Failure to respond is indicated by any of:

- Reduced level of consciousness despite resuscitation
- Heart rate or respiratory rate fulfil high risk criteria
- Lactate over 2 mmol/litre after 1 hour

Give parenteral antibiotics to infants aged under 3 months as follows:

- Infants younger than 1 month with fever
- All infants aged 1 to 3 months with fever who appear unwell
- Infants aged 1 to 3 months with white blood cell count less than 5×10^9/litre or greater than 15×10^9/litre

(This recommendation is from NICE's guideline on fever in under 5s [see the NGC summary of the NICE guideline Feverish illness in children: assessment and initial management in children younger than 5 years].)

Children Aged under 5 Years with Suspected Sepsis Who Meet 2 or More Moderate to High Risk Criteria

For children aged under 5 years with suspected sepsis and 2 or more moderate to high risk criteria:

- Carry out a venous blood test for the following:
  - Blood gas, including glucose and lactate measurement
  - Blood culture
  - Full blood count
  - C-reactive protein
  - Urea and electrolytes
  - Creatinine

- Arrange for a clinician[6] to review the person's condition and venous lactate results within 1 hour of meeting 2 or more moderate to high risk criteria in an acute hospital setting

For children aged under 5 years with suspected sepsis who meet 2 or more moderate to high risk criteria and have lactate over 2 mmol/litre, treat as high risk and follow recommendations under "Children Aged under 5 Years with Suspected Sepsis Who Meet 1 or More High Risk Criteria," above.

For children aged under 5 years with suspected sepsis who meet 2 or more moderate to high risk criteria, have lactate of less than 2 mmol/litre, and in whom a definitive condition cannot be identified:

- Repeat structured assessment at least hourly
- Ensure review by a senior clinical decision maker[11] within 3 hours of meeting 2 or more moderate to high risk criteria in an acute hospital setting for consideration of antibiotics

For children aged under 5 years with suspected sepsis who meet 2 or more moderate to high risk criteria, have lactate of less than 2 mmol/litre, and in whom a definitive condition or infection can be identified and treated:

- Manage the definitive condition, and
- If appropriate, discharge with information depending on the setting (see "Information at Discharge for People Assessed for Suspected Sepsis, But Not Diagnosed with Sepsis," below)

Children under 5 Years with Suspected Sepsis Who Meet Only 1 Moderate to High Risk Criterion

For children aged under 5 years with suspected sepsis who meet only 1 moderate to high risk criterion:

- Arrange clinician review within 1 hour of meeting a moderate to high risk criterion for clinical assessment, and
- Perform blood tests if indicated

For children aged under 5 years with suspected sepsis who meet only 1 moderate to high risk criterion and in whom a definitive condition can be identified and treated:

- Manage the definitive condition
- If appropriate, discharge with information depending on the setting (see "Information at Discharge for People Assessed for Suspected Sepsis, But Not Diagnosed with Sepsis," below)

For children aged under 5 years with suspected sepsis who meet only 1 moderate to high risk criterion and in whom a definitive condition cannot be identified:

- Repeat structured assessment at least hourly
- Ensure review by a senior clinical decision maker[11] within 3 hours of meeting a moderate to high risk criterion in an acute hospital setting for consideration of antibiotics

Children Aged under 5 Years with Suspected Sepsis and No High Risk or Moderate to High Risk Criteria

Arrange clinical assessment[8] of children aged under 5 years who have suspected sepsis and no high risk or moderate to high risk criteria and manage according to clinical judgement.

Antibiotic Treatment in People with Suspected Sepsis

Pre-alert secondary care (through general practitioner [GP] or ambulance service) when any high risk criteria are met in a person with suspected sepsis outside of an acute hospital, and transfer them immediately.

Ensure urgent assessment mechanisms are in place to deliver antibiotics when any high risk criteria are met in secondary care (within 1 hour of meeting a high risk criterion in an acute hospital setting).

Ensure GPs and ambulance services have mechanisms in place to give antibiotics for people with high risk criteria in pre-hospital settings in locations where transfer time is more than 1 hour.

For patients in hospital who have suspected infections, take microbiological samples before prescribing an antimicrobial and review the prescription when the results are available. For people with suspected sepsis take blood cultures before antibiotics are given. (This

recommendation is adapted from NICE's guideline on antimicrobial stewardship .)

If meningococcal disease is specifically suspected (fever and purpuric rash) give appropriate doses of parenteral benzyl penicillin in community settings and intravenous ceftriaxone in hospital settings. (This recommendation is adapted from NICE's guideline on meningitis [bacterial] and meningococcal septicaemia in under 16s .)

For all people with suspected sepsis where the source of infection is clear use existing local antimicrobial guidance.

For people aged 18 years and over who need an empirical intravenous antimicrobial for a suspected infection but who have no confirmed diagnosis, use an intravenous antimicrobial from the agreed local formulary and in line with local (where available) or national guidelines. (This recommendation is adapted from NICE's guideline on antimicrobial stewardship .)

For people aged up to 17 years (for neonates see recommendation below) with suspected community acquired sepsis of any cause give ceftriaxone 80 mg/kg once a day with a maximum dose of 4 g daily at any age. (This recommendation is adapted from NICE's guideline on meningitis [bacterial] and meningococcal septicaemia in under 16s .)

For people aged up to 17 years with suspected sepsis who are already in hospital, or who are known to have previously been infected with or colonised with ceftriaxone-resistant bacteria, consult local guidelines for choice of antibiotic.

For children younger than 3 months, give an additional antibiotic active against listeria (for example, ampicillin or amoxicillin). (This recommendation is adapted from NICE's guideline on fever in under 5s [see the NGC summary of the NICE guideline Feverish illness in children: assessment and initial management in children younger than 5 years].)

Treat neonates presenting in hospital with suspected sepsis in their first 72 hours with intravenous benzylpenicillin and gentamicin. (This recommendation is adapted from NICE's guideline on neonatal infection [see the NGC summary of the NICE guideline Antibiotics for early-onset neonatal infection. Antibiotics for the prevention and treatment of early-onset neonatal infection].)

Treat neonates who are more than 40 weeks corrected gestational age who present with community acquired sepsis with ceftriaxone 50 mg/kg unless already receiving an intravenous calcium infusion at the time. If 40 weeks corrected gestational age or below or receiving an intravenous calcium infusion use cefotaxime 50 mg/kg every 6 to 12 hours, depending on the age of the neonate.

Follow the recommendations in NICE's guideline on antimicrobial stewardship: systems and processes for effective antimicrobial medicine when prescribing and using antibiotics to treat people with suspected or confirmed sepsis.

Intravenous Fluids in People with Suspected Sepsis

If patients over 16 years need intravenous fluid resuscitation, use crystalloids that contain sodium in the range 130–154 mmol/litre with a bolus of 500 ml over less than 15 minutes. (This recommendation is from NICE's guideline on intravenous fluid therapy in adults in hospital [see the NGC summary of the NICE guideline Intravenous fluid therapy in adults in hospital].)

If children and young people up to 16 years need intravenous fluid resuscitation, use glucose-free crystalloids that contain sodium in the range 130–154 mmol/litre, with a bolus of 20 ml/kg over less than 10 minutes. Take into account preexisting conditions (for example, cardiac disease or kidney disease), because smaller fluid volumes may be needed. (This recommendation is from NICE's guideline on intravenous fluid therapy in children and young people in hospital [see the NGC summary of the NICE guideline Intravenous fluid therapy in children and young people in hospital].)

If neonates need intravenous fluid resuscitation, use glucose-free crystalloids that contain sodium in the range 130–154 mmol/litre, with a bolus of 10–20 ml/kg over less than 10 minutes. (This recommendation is from NICE's guideline on intravenous fluid therapy in children and young people in hospital [see the NGC summary of the NICE guideline Intravenous fluid therapy in children and young people in hospital].)

Reassess the patient after completion of the intravenous fluid bolus, and if no improvement give a second bolus. If there is no improvement after a second bolus alert a consultant to attend (in line with recommendations under "Managing and Treating Suspected Sepsis in Acute Hospital Settings," above).

Use a pump, or syringe if no pump is available, to deliver intravenous fluids for resuscitation to children under 12 years with suspected sepsis who need fluids in bolus form.

If using a pump or flow controller to deliver intravenous fluids for resuscitation to people over 12 years with suspected sepsis who need fluids in bolus form ensure device is capable of delivering fluid at required rate, for example at least 2000 ml/hour in adults.

Do not use starch based solutions or hydroxyethyl starches for fluid resuscitation for people with sepsis. (This recommendation is adapted from NICE's guidelines on intravenous fluid therapy in adults in hospital and intravenous therapy in children and young people in hospital [see the NGC summaries of the NICE guidelines Intravenous fluid therapy in adults in hospital and Intravenous fluid therapy in children and young people in hospital].)

Consider human albumin solution 4% to 5% for fluid resuscitation only in patients with sepsis and shock. (This recommendation is adapted from NICE's guideline on intravenous fluid therapy in adults in hospital [see the NGC summary of the NICE guideline Intravenous fluid therapy in adults in hospital].)

Using Oxygen in People with Suspected Sepsis

Give oxygen to achieve a target saturation of 94% to 98% for adult patients or 88% to 92% for those at risk of hypercapnic respiratory failure.

Oxygen should be given to children with suspected sepsis who have signs of shock or oxygen saturation (SpO_2) of less than 91% when breathing air. Treatment with oxygen should also be considered for children with an SpO_2 of greater than 92%, as clinically indicated. (This recommendation is adapted from NICE's guideline on fever in under 5s [see the NGC summary of the NICE guideline Feverish illness in children: assessment and initial management in children younger than 5 years].)

Finding the Source of Infection in People with Suspected Sepsis

Carry out a thorough clinical examination to look for sources of infection, including sources that might need surgical drainage, as part of the initial assessment.

Tailor investigations of the sources of infection to the person's clinical history and findings on examination.

Consider urine analysis and chest X-ray to identify the source of infection in all people with suspected sepsis.

Consider imaging of the abdomen and pelvis if no likely source of infection is identified after clinical examination and initial tests.

Involve the adult or paediatric surgical and gynaecological teams early on if intra-abdominal or pelvic infection is suspected in case surgical treatment is needed.

Do not perform a lumbar puncture without consultant instruction if any of the following contraindications are present:

- Signs suggesting raised intracranial pressure or reduced or fluctuating level of consciousness (Glasgow Coma Scale score less than 9 or a drop of 3 points or more)
- Relative bradycardia and hypertension
- Focal neurological signs
- Abnormal posture or posturing
- Unequal, dilated or poorly responsive pupils
- Papilloedema
- Abnormal 'doll's eye' movements
- Shock
- Extensive or spreading purpura
- After convulsions until stabilised
- Coagulation abnormalities or coagulation results outside the normal range or platelet count below $100x10^9$/litre or receiving anticoagulant therapy
- Local superficial infection at the lumbar puncture site
- Respiratory insufficiency in children

(This recommendation is adapted from NICE's guideline on meningitis [bacterial] and meningococcal septicaemia in under 16s .)

Perform lumbar puncture in the following children with suspected sepsis (unless contraindicated; see contraindications in the recommendation above).

- Infants younger than 1 month
- All infants aged 1 to 3 months who appear unwell
- Infants aged 1 to 3 months with a white blood cell count less than 5×10^9/litre or greater than 15×10^9/litre

(This recommendation is adapted from NICE's guideline on fever in under 5s [see the NGC summary of the NICE guideline Feverish illness in children: assessment and initial management in children younger than 5 years].)

Information and Support for People with Sepsis and Their Families and Carers

People Who Have Sepsis and Their Families and Carers

Ensure a care team member is nominated to give information to families and carers, particularly in emergency situations such as in the emergency department. This should include:

- An explanation that the person has sepsis, and what this means
- An explanation of any investigations and the management plan
- Regular and timely updates on treatment, care and progress

Ensure information is given without using medical jargon. Check regularly that people understand the information and explanations they are given.

Give people with sepsis and their family members and carers opportunities to ask questions about diagnosis, treatment options, prognosis and complications. Be willing to repeat any information as needed.

Give people with sepsis and their families and carers information about national charities and support groups that provide information about sepsis and the causes of sepsis.

Information at Discharge for People Assessed for Suspected Sepsis, But Not Diagnosed with Sepsis

Give people who have been assessed for sepsis but have been discharged without a diagnosis of sepsis (and their family or carers, if appropriate) verbal and written information about:

- What sepsis is, and why it was suspected
- What tests and investigations have been done
- Instructions about which symptoms to monitor
- When to get medical attention if their illness continues
- How to get medical attention if they need to seek help urgently

Confirm that people understand the information they have been given, and what actions they should take to get help if they need it.

Information at Discharge for People at Increased Risk of Sepsis

Ensure people who are at increased risk of sepsis (for example after surgery) are told before discharge about symptoms that should prompt them to get medical attention and how to get it.

See NICE's guideline on neutropenic sepsis for information for people with neutropenic sepsis [see the NGC summary of the NICE guideline Neutropenic sepsis: prevention and management of neutropenic sepsis in cancer patients].)

Information at Discharge for People Who Have Had Sepsis

Ensure people and their families and carers, if appropriate, have been informed that they have had sepsis.

Ensure discharge notifications to GPs include the diagnosis of sepsis.

Give people who have had sepsis (and their families and carers, when appropriate) opportunities to discuss their concerns. These may include:

- Why they developed sepsis
- Whether they are likely to develop sepsis again
- If more investigations are necessary
- Details of any community care needed, for example, related to peripherally inserted central venous catheters (PICC) lines or other intravenous catheters
- What they should expect during recovery
- Arrangements for follow-up, including specific critical care follow up if relevant
- Possible short-term and long-term problems

Give people who have had sepsis and their families and carers information about national charities and support groups that provide information

about sepsis and causes of sepsis.

Advise carers they have a legal right to have a carer's assessment of their needs, and give them information on how they can get this.

See NICE's guideline on rehabilitation after critical illness in adults for recommendations on rehabilitation and follow up after critical illness.

See NICE's guideline on meningitis (bacterial) and meningococcal septicaemia in under 16s for follow up of people who have had meningococcal septicaemia.

Training and Education

Ensure all healthcare staff and students involved in assessing people's clinical condition are given regular, appropriate training in identifying people who might have sepsis. This includes primary, community care and hospital staff including those working in care homes.

Ensure all healthcare professionals involved in triage or early management are given regular appropriate training in identifying, assessing and managing sepsis. This should include:

- Risk stratification strategies
- Local protocols for early treatments, including antibiotics and intravenous fluids
- Criteria and pathways for escalation, in line with their health care setting

Footnotes

[1]Emergency care requires facilities for resuscitation to be available and depending on local services may be emergency department, medical admissions unit and for children may be paediatric ambulatory unit or paediatric medical admissions unit.

[2]A 'senior clinical decision maker' for people aged 18 years or over should be someone who is authorised to prescribe antibiotics, such as a doctor of grade CT3/ST3 or above or equivalent, such as an advanced nurse practitioner with antibiotic prescribing responsibilities, depending on local arrangements. A 'senior decision maker' for people aged 12 to 17 years is a paediatric or emergency care qualified doctor of grade ST4 or above or equivalent.

[3]Appropriate consultant may be the consultant under whom the patient is admitted or a consultant covering acute medicine, anaesthetics.

[4]Referral may be a formal referral process or discussion with specialist in intensive care or intensive care outreach team.

[5]Critical care means an intensivist or intensive care outreach team, or specialist in intensive care or paediatric intensive care.

[6]A 'clinician' should be a medically qualified practitioner or equivalent who has antibiotic prescribing responsibilities.

[7]For definition of acute kidney injury, see NICE's guideline on acute kidney injury (see the NGC summary of Acute kidney injury. Prevention, detection and management of acute kidney injury up to the point of renal replacement therapy).

[8]Clinical assessment should be carried out by a medically qualified practitioner or equivalent who has antibiotic prescribing responsibilities.

[9]A 'senior clinical decision maker' for children aged 5 to 11 years is a paediatric or emergency care doctor of grade ST4 or above or equivalent.

[10]This should be by a medically qualified practitioner or equivalent with prescribing responsibilities.

[11]A 'senior clinical decision maker' for children aged under 5 years is a paediatric qualified doctor of grade ST4 or above.

Definitions

Strength of Recommendations

Some recommendations can be made with more certainty than others. The Guideline Development Group (GDG) makes a recommendation based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. For some interventions, the GDG is confident that, given the information it has looked at, most patients would choose the intervention. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the strength of the recommendation).

Interventions That Must (or Must Not) Be Used

The GDG usually uses 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally 'must' (or 'must not') is used if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Interventions That Should (or Should Not) Be Used – a 'Strong' Recommendation

The GDG uses 'offer' (and similar words such as 'refer' or 'advise') when confident that, for the vast majority of patients, an intervention will do

more good than harm, and be cost effective. Similar forms of words (for example, 'Do not offer…') are used when the GDG is confident that an intervention will not be of benefit for most patients.

Interventions That Could Be Used

The GDG uses 'consider' when confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

Clinical Algorithm(s)

The following clinical algorithms are provided on the National Institute for Health and Care Excellence (NICE) Web site :

- Algorithm for managing suspected sepsis in adults and young people aged 18 years and over in an acute hospital setting
- Algorithm for managing suspected sepsis in adults and young people aged 18 years and over outside an acute hospital setting
- Algorithm for managing suspected sepsis in children aged 5–11 years in an acute hospital setting
- Algorithm for managing suspected sepsis in children aged 5–11 years outside an acute hospital setting
- Algorithm for managing suspected sepsis in children aged under 5 years in an acute hospital setting
- Algorithm for managing suspected sepsis in children aged under 5 years outside an acute hospital setting
- Algorithm for managing suspected sepsis in children and young people aged 12–17 years in an acute hospital setting
- Algorithm for managing suspected sepsis in children and young people aged 12–17 years outside an acute hospital setting

In addition, a NICE pathway titled "Sepsis overview" is provided on the NICE Web site .

Scope

Disease/Condition(s)

Sepsis including septic shock

Guideline Category

Diagnosis

Evaluation

Management

Risk Assessment

Treatment

Clinical Specialty

Critical Care

Emergency Medicine

Family Practice

Geriatrics

Infectious Diseases

Internal Medicine

Obstetrics and Gynecology

Pediatrics

Intended Users

Advanced Practice Nurses

Allied Health Personnel

Emergency Medical Technicians/Paramedics

Health Care Providers

Hospitals

Nurses

Patients

Physician Assistants

Physicians

Public Health Departments

Guideline Objective(s)

- To ensure healthcare systems in all clinical settings consider sepsis as an immediate life-threatening condition that should be recognised and treated as an emergency
- To outline the immediate actions required for those with suspicion of sepsis and who are at highest risk of morbidity and mortality from sepsis
- To provide a framework for risk assessment, treatment and follow-up or 'safety-netting' of people not requiring immediate resuscitation
- To ensure that all people with sepsis due to any cause are recognised and initial treatment initiated before definitive treatment on other specific pathways is instituted

Target Population

All populations with suspected or confirmed sepsis, their families and carers

Interventions and Practices Considered

Diagnosis/Evaluation/Risk Assessment

1. Identifying people at increased risk of sepsis
2. Use of scoring systems
3. Assessment of physiological signs and symptoms
    - Heart rate
    - Respiratory rate
    - Blood pressure
    - Level of consciousness
    - Oxygen saturation
    - Capillary refill time
    - Temperature

    - Urine output
    - Skin appearance
    - Behaviour
    - Mental state, cognitive state
4. Risk stratification

Management/Treatment

1. Managing suspected sepsis outside acute hospital settings
    - Referral to emergency care
    - Assessment of condition
2. Managing and treating suspected sepsis in acute hospital settings
    - Blood tests for diagnosis of sepsis (blood gases, glucose, lactate, blood culture, full blood count, urea and electrolytes, creatinine, clotting screen, C-reactive protein)
    - Antimicrobial treatments
    - Intravenous fluid administration
    - Escalation of care (e.g., direction to senior healthcare professional or critical care provider)
3. Use of inotropic agents and vasopressors
4. Use of supplemental oxygen
5. Monitoring
6. Finding source of infection
    - Clinical investigations
    - Urinalysis
    - X-ray and other imaging
    - Lumbar puncture
7. Providing information, education, and support to patients, families, and carers
8. Education and training programmes to improve recognition, diagnosis, and management of sepsis

Note: The following are considered but not recommended: assessment for disseminated intravascular coagulation, use of bicarbonate for acid-base balance, early goal-directed therapy (EGDT).

Major Outcomes Considered

- Sensitivity, specificity, positive and negative predictive value of diagnostic tests
- 28-day mortality rate
- Clinical resolution
- Health-related quality of life
- Critical care admission
- Progression to severe sepsis
- Treatment failure
- Appropriate or inappropriate use of antibiotics
- Duration of treatment
- Hospital re-admission
- Length of hospital stay
- Complications
- Admission to critical care as a proxy for progression to severe sepsis
- Duration of critical care stay
- Number of organs supported
- Adverse events
- Patient satisfaction, including understanding
- Reduction in time to diagnosis
- Time to shock reversal

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): The guideline was developed by the National Guideline Centre on behalf of the National Institute for Health and Care Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance and related appendices.

Developing the Review Questions and Outcomes

Review questions were developed in a PICO framework (patient, intervention, comparison and outcome) for intervention reviews; in a framework of population, index tests, reference standard and target condition for reviews of diagnostic test accuracy; and using population, presence or absence of factors under investigation (for example, prognostic factors) and outcomes for prognostic reviews.

This use of a framework guided the literature searching process, critical appraisal and synthesis of evidence, and facilitated the development of recommendations by the Guideline Development Group (GDG). The review questions were drafted by the NGC technical team and refined and validated by the GDG. The questions were based on the key clinical areas identified in the scope (see Appendix A).

A total of 18 review questions were identified.

Full literature searches, critical appraisals and evidence reviews were completed for all the specified review questions, except for source of infection, early goal-directed therapy (EGDT) and central venous (CV) access. The recommendations for source of infection and CV access are based on discussions, consensus and expert opinion of the GDG and were also informed by other review questions. The rationale for these decisions is explained in more detail in relevant chapters of the full version of the guideline. The review on EGDT only includes a recent systematic review on three large multi-centre randomised controlled trials (RCTs), the ProMISe, ARISE, and ProCESS trials. This systematic review was considered to adequately address the EDGT review question.

Searching for Evidence

Clinical Literature Search

Systematic literature searches were undertaken to identify all published clinical evidence relevant to the review questions. Searches were undertaken according to the parameters stipulated within the NICE guidelines (see the "Availability of Companion Documents" field). Databases were searched using relevant medical subject headings, free-text terms and study-type filters where appropriate. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in English. All searches were conducted in MEDLINE, EMBASE, and The Cochrane Library. Additional subject specific databases were used for one question: CINAHL and PsycINFO for information support. All searches were updated on 9 October 2015. No papers added to the databases after this date were considered.

Search strategies were quality assured by cross-checking reference lists of highly relevant papers, analysing search strategies in other systematic reviews, and asking GDG members to highlight any additional studies. The questions, the study types applied, the databases searched and the years covered can be found in Appendix G of the full version of the guideline.

The titles and abstracts of records retrieved by the searches were sifted for relevance, with potentially significant publications obtained in full text. These were assessed against the inclusion criteria.

During the scoping stage, a search was conducted for guidelines and reports on the Web sites listed below from organisations relevant to the topic. Searching for unpublished literature was not undertaken. All references sent by stakeholders were considered.

- Guidelines International Network database (www.g-i-n.net)
- National Health Service (NHS) Evidence Search (www.evidence.nhs.uk)
- TRIP database (https://www.tripdatabase.com/)
- Sepsis Alliance (http://www.sepsisalliance.org /)
- The UK Sepsis Trust (http://sepsistrust.org /)

- Center for Sepsis Control & Care (http://www.cscc.uniklinikum-jena.de/cscc/en/CSCC-p-7.html)

Health Economic Literature Search

Systematic literature searches were also undertaken to identify health economic evidence within published literature relevant to the review questions. The evidence was identified by conducting a broad search relating to sepsis and bacterial meningitis populations in the NHS Economic Evaluation Database (NHS EED), the Health Technology Assessment database (HTA) and the Health Economic Evaluations Database (HEED) with no date restrictions. The Health Economic Evaluation Database ceased production in 2014 with access ceasing in January 2015. Additionally, the search was run on MEDLINE and EMBASE using a specific economic filter, from 2012, to ensure recent publications that had not yet been indexed by the economic databases were identified. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in English.

The health economic search strategies are included in Appendix G. All searches were updated on 9 October 2015. No papers added to the databases after this date were considered.

Evidence of Effectiveness

The evidence was reviewed following the steps shown schematically in Figure 1 in the full version of the guideline document:

- Potentially relevant studies were identified for each review question from the relevant search results by reviewing titles and abstracts. Full papers were then obtained.
- Full papers were reviewed against pre-specified inclusion and exclusion criteria to identify studies that addressed the review question in the appropriate population (review protocols are included in Appendix C of the full version of the guideline).

A 20% sample of each of the stages of the reviewing process was quality assured by a second reviewer to eliminate any potential of reviewer bias or error.

Inclusion and Exclusion Criteria

The inclusion and exclusion of studies was based on the review protocols, which can be found in Appendix C. Excluded studies by review question (with the reasons for their exclusion) are listed in Appendix L. The GDG was consulted about any uncertainty regarding inclusion or exclusion.

The guideline population was defined to be adults, children (including neonates) and young people at risk of developing sepsis. For some review questions, the review population also included people with definite sepsis, severe sepsis or septic shock. The review on information and support also included families and carers of people who had sepsis or severe sepsis, and people who had survived episodes of severe sepsis. For the review on education and training, the review population was defined as all healthcare professionals involved in the diagnosis, management and monitoring of sepsis.

The subgroups considered included children, adults, pregnant women, people at higher risk of infection, and different settings of care delivery. For some review questions, the evidence was grouped by predefined subgroup analysis based on severity of illness.

Randomised trials, non-randomised trials, and observational studies (including diagnostic or prognostic studies) were included in the evidence reviews as appropriate.

Literature reviews, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded. The review protocols are presented in Appendix C.

Evidence of Cost-effectiveness

The GDG is required to make decisions based on the best available evidence of both clinical and cost-effectiveness. Guideline recommendations should be based on the expected costs of the different options in relation to their expected health benefits (that is, their "cost effectiveness") rather than the total implementation cost. Thus, if the evidence suggests that a strategy provides significant health benefits at an acceptable cost per patient treated, it should be recommended even if it would be expensive to implement across the whole population.

Evidence on cost-effectiveness related to the key clinical issues being addressed in the guideline was sought. The health economist:

- Undertook a systematic review of the published economic literature.

Literature Review

The health economist:

- Identified potentially relevant studies for each review question from the economic search results by reviewing titles and abstracts. Full papers were then obtained.
- Reviewed full papers against pre-specified inclusion and exclusion criteria to identify relevant studies (see below for details).

Inclusion and Exclusion Criteria

Full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost–utility, cost-effectiveness, cost–benefit and cost–consequences analyses) and comparative costing studies that addressed the review question in the relevant population were considered potentially includable as economic evidence.

Studies that only reported cost per hospital (not per patient), or only reported average cost-effectiveness without disaggregated costs and effects, were excluded. Literature reviews, abstracts, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded. Studies published before 1999 and studies from non-Organisation for Economic Co-operation and Development (OECD) countries or the USA were also excluded, on the basis that the applicability of such studies to the present UK NHS context is likely to be too low for them to be helpful for decision-making.

Remaining studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high quality, directly applicable UK analysis was available, then other less relevant studies may not have been included. Where exclusions occurred on this basis, this is noted in the relevant section in the full version of the guideline.

For more details about the assessment of applicability and methodological quality see Table 7 in the full version of the guideline and the economic evaluation checklist (Appendix G of the NICE guidelines manual 2012) and the health economics review protocol in Appendix C.

Number of Source Documents

Refer to the article selection reviews in the full guideline appendices (Appendix E for clinical articles and Appendix F for economic articles [see the "Availability of Companion Documents" field]) for flow charts and detailed information on the total number of studies identified, selected, and excluded for each guideline topic.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Overall Quality of Outcome Evidence in Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Level	Description
High	Further research is very unlikely to change confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very Low	Any estimate of effect is very uncertain.

Methods Used to Analyze the Evidence

Meta-Analysis

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): The guideline was developed by the National Guideline Centre on behalf of the National Institute for Health and Care Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance and related appendices.

Evidence of Effectiveness

The evidence was reviewed following the steps shown schematically in Figure 1 of the full version of the guideline:

- Relevant studies were critically appraised using the appropriate checklist as specified in the NICE guidelines manual (see the "Availability of Companion Documents" field).
- Key information was extracted on the study's methods, PICO (patient, intervention, comparison and outcome) factors and results. These were presented in summary tables (in each review chapter of the full version of the guideline) and evidence tables (in Appendix H).
- Summaries of evidence were generated by outcome (included in the relevant review chapters) and were presented in Guideline Development Group (GDG) meetings:
    - Randomised studies: data were meta-analysed where appropriate and reported in Grading of Recommendations Assessment, Development and Evaluation (GRADE) profiles (for intervention reviews)
    - Observational studies: data were presented as a range of values in GRADE profiles.
    - Prognostic studies: data were presented as a range of values, usually in terms of the relative effect as reported by the authors
    - Diagnostic studies: for reviews of diagnostic tests, diagnostic randomised controlled trials (RCTs) were the first line approach and, as with intervention reviews, evidence summaries were generated. If no evidence was found from diagnostic RCTs, diagnostic accuracy studies were reviewed. Coupled sensitivity and specificity values were summarised in forest plots. Accuracy measures were meta-analysed and reported as pooled results where appropriate. Where meta-analysis was performed, coupled sensitivity and specificity values were also presented on summary receiver operating characteristic (sROC) plots along with the results of the meta-analysis (the summary sensitivity and specificity point and 95% confidence region) and the summary curve. Where evidence was not meta-analysed, because studies differed in population or outcome, then no alternative pooling strategies were carried out, on the basis that such pooling would have little meaning. Results from single studies were presented.
    - Qualitative studies: each study was summarised in a table where possible, otherwise presented in a narrative.

A 20% sample of each of the above stages of the reviewing process was quality assured by a second reviewer to eliminate any potential of reviewer bias or error.

Methods of Combining Clinical Studies

Data Synthesis for Intervention Reviews

Where possible, meta-analyses were conducted to combine the results of studies for each review question using Cochrane Review Manager (RevMan5) software. Fixed-effects (Mantel-Haenszel) techniques were used to calculate risk ratios (relative risk) for the binary outcomes, such as mortality, critical care admission and adverse events.

For continuous outcomes, measures of central tendency (mean) and variation (standard deviation) were required for meta-analysis. Data for continuous outcomes, such as health-related quality of life, length of stay in intensive care unit (ICU) or hospital, and the number of organs supported, were analysed using an inverse variance method for pooling weighted mean differences and, where the studies had different scales, standardised mean differences were used. A generic inverse variance option in RevMan5 was used if any studies reported solely the summary statistics and 95% confidence interval (95% CI) or standard error; this included any hazard ratios reported. However, in cases where standard deviations were not reported per intervention group, the standard error (SE) for the mean difference was calculated from other reported statistics (p values or 95% CIs); meta-analysis was then undertaken for the mean difference and SE using the generic inverse variance method in RevMan5. When the only evidence was based on studies that summarised results by presenting medians (and interquartile ranges), or only p values were given, this information was assessed in terms of the study's sample size and was included in the GRADE tables without calculating the relative or absolute effects. Consequently, aspects of quality assessment such as imprecision of effect could not be assessed for evidence of this type.

Data Synthesis for Prognostic Factor Reviews

A variety of prognostic effect measures were extracted from papers, depending on the type of outcome.

For binary outcomes, odds ratios, risk ratios or hazard ratios (with their 95% CIs) for the independent effect of each prognostic factor on the outcome were extracted. Beta coefficients for dichotomous outcomes were normally converted to an odds ratio (OR) by taking the anti-natural

logarithm of the beta coefficient (as Beta coefficient = ln OR).

For continuous outcomes, the Beta coefficients (or standardised beta coefficients) with their 95% CIs for the independent effect of each prognostic factor were extracted.

RCTs, pooled analyses of patient level data, and prospective or retrospective cohort studies were included. Case-control studies were excluded because of their high risk of recall bias. All non-RCT studies were required to have considered all key confounders previously identified by the GDG at the protocol stage for that outcome. Studies not considering these key confounders were excluded. For a confounder to be regarded as having been adequately considered, it would have to have been included in the multivariable analysis (although in a step-wise model it would not necessarily have to be present in the final model) or would have to have been shown to be matched across risk factor or outcome groups at baseline.

Data Synthesis for Diagnostic Test Accuracy Reviews

For the reviews of diagnostic accuracy, the following measures were used:

The coupled sensitivity and specificity values at a given threshold: Coupled forest plots of sensitivity and specificity with their 95% CIs across studies were produced for each test (and for each clinically relevant threshold), using RevMan5. In order to do this, 2×2 tables (the number of true positives, false positives, true negatives and false negatives) were directly taken from the study where possible, or else were derived from raw data or calculated from the set of test accuracy statistics.

Data were meta-analysed when data were available from 3 or more studies (given data were reported at the same threshold or within a defined range of similar thresholds). To do this, data were entered into a bivariate model using WinBUGS. If the model did not converge due to heterogeneity, the pooled estimate was not presented. A diagnostic meta-analysis was not conducted because the included population and the patient outcomes in the included studies were too different from each other. Where meta-analysis was performed, in addition to the forest plots, the coupled sensitivity and specificity values were also presented on summary receiver operating characteristic (sROC) plots for visual information along with the results of the meta-analysis (the summary sensitivity and specificity point and 95% confidence region) and the summary curve. To do this, bivariate WinBUGS model outputs were entered into RevMan5.

Pooled sensitivity and specificity values were reported in the clinical evidence profile tables (or, if meta-analysis was not performed, results from single studies were presented). For comparison of multiple index tests (or between different thresholds for the same test), the sensitivity and specificity values were compared between tests.

Data Synthesis for Qualitative Study Reviews

Where possible a meta-synthesis was conducted to combine qualitative study results. This guideline includes two qualitative review questions; one on information, education and support considered to be useful by people who are at risk of developing sepsis, have sepsis or have survived episodes of sepsis, and one on the availability of education training programmes for healthcare professionals to recognise, diagnose and manage sepsis. Whenever studies identified a qualitative theme, this was extracted and the main characteristics were summarised. When all themes were extracted from studies, common concepts were categorised and tabulated. This included information on how many studies had identified this theme. A frequently identified theme may indicate an important issue for the review, but frequency of theme is not the only indicator of importance. Study type and population in qualitative research can differ widely meaning that themes that may only be identified by one or a few studies can provide important new information. Therefore for the purpose of the qualitative review in this guideline the categorisation of themes was exhaustive, that is all themes were accounted for in the synthesis. The GDG could then draw conclusions on the relative merits of each of the themes and how they may help in forming recommendations.

See Section 4.3.2 in the full version of the guideline document for additional information on data synthesis for different types of studies.

Appraising the Quality of Evidence by Outcomes

Interventional Studies

The evidence for outcomes from the included RCTs and, where appropriate, observational studies were evaluated and presented using an adaptation of the 'GRADE toolbox' developed by the international GRADE working group (www.gradeworkinggroup.org). The software developed by the GRADE working group (GRADEpro) was used to assess the quality of each outcome, taking into account individual study quality factors and the meta-analysis results. Results were presented in GRADE profiles 'GRADE tables'), which consist of 2 sections: the 'Clinical evidence profile' table includes details of the quality assessment while the 'Clinical evidence summary of findings' table includes pooled outcome data, where appropriate, an absolute measure of intervention effect and the summary of quality of evidence for that outcome. In this table, the columns for intervention and control indicate summary measures and measures of dispersion (such as mean and

standard deviation or median and range) for continuous outcomes and frequency of events (n/N: the sum across studies of the number of patients with events divided by sum of the number of completers) for binary outcomes. Reporting or publication bias was only taken into consideration in the quality assessment and included in the 'Clinical evidence profile' table if it was apparent.

The evidence for each outcome was examined separately for the quality elements listed and defined in Table 2 of the full version of the guideline. Each element was graded using the quality levels listed in Table 3 of the full version of the guideline. The main criteria considered in the rating of these elements are discussed below. Footnotes were used to describe reasons for grading a quality element as having serious or very serious problems. The ratings for each component were summed to obtain an overall assessment for each outcome (see the "Rating Scheme for the Strength of the Evidence" field).

The GRADE toolbox is currently designed only for randomised trials and observational studies but the quality assessment elements and outcome presentation were adapted for diagnostic accuracy studies.

Grading the Quality of Clinical Evidence

After results were pooled, the overall quality of evidence for each outcome was considered. The following procedure was adopted when using GRADE:

1. A quality rating was assigned, based on the study design. RCTs started as High, observational studies as Low, and uncontrolled case series as Low or Very low.
2. The rating was then downgraded for the specified criteria: risk of bias (study limitations), inconsistency, indirectness, imprecision and publication bias. These criteria are detailed in the full version of the guideline. Evidence from observational studies (which had not previously been downgraded) was upgraded if there was: a large magnitude of effect, a dose–response gradient, and if all plausible confounding would reduce a demonstrated effect or suggest a spurious effect when results showed no effect. Each quality element considered to have 'serious' or 'very serious' risk of bias was rated down by 1 or 2 points respectively.
3. The downgraded or upgraded marks were then summed and the overall quality rating was revised. For example, all RCTs started as High and the overall quality became Moderate, Low or Very low if 1, 2 or 3 points were deducted respectively.
4. The reasons or criteria used for downgrading were specified in the footnotes.

The details of the criteria used for each of the main quality elements for all types of studies are discussed further in Sections 4.3.4.1.1 to 4.3.4.1.4 of the full version of the guideline. Refer to Sections 4.3.4.2 and 4.3.4.3 for information on diagnostic and prognostic studies, respectively.

Assessing Clinical Importance

The GDG assessed the evidence by outcome in order to determine if there was, or potentially was, a clinically important benefit, a clinically important harm or no clinically important difference between interventions. To facilitate this, binary outcomes were converted into absolute risk differences (ARDs) using GRADEpro software: the median control group risk across studies was used to calculate the ARD and its 95% CI from the pooled risk ratio.

The assessment of benefit, harm, or no benefit or harm was based on the point estimate of absolute effect for intervention studies which was standardised across the reviews. The GDG considered for most of the outcomes in the intervention reviews that if at least 100 participants per 1000 (10%) achieved (if positive) the outcome of interest in the intervention group compared to the comparison group then this intervention would be considered beneficial. The same point estimate but in the opposite direction would apply if the outcome was negative.

This assessment was carried out by the GDG for each critical outcome, and an evidence summary table was produced to compile the GDG's assessments of clinical importance per outcome, alongside the evidence quality and the uncertainty in the effect estimate (imprecision).

Evidence Statements

Evidence statements are summary statements that are presented after the GRADE profiles, summarising the key features of the clinical effectiveness evidence presented. The wording of the evidence statements reflects the certainty or uncertainty in the estimate of effect. The evidence statements encompass the following key features of the evidence:

- An indication of the direction of effect (if one treatment is beneficial or harmful compared to the other, or whether there is no difference between the 2 tested treatments)
- A description of the overall quality of evidence

Evidence of Cost-effectiveness

The GDG is required to make decisions based on the best available evidence of both clinical and cost-effectiveness. Guideline recommendations

should be based on the expected costs of the different options in relation to their expected health benefits (that is, their "cost effectiveness") rather than the total implementation cost. Thus, if the evidence suggests that a strategy provides significant health benefits at an acceptable cost per patient treated, it should be recommended even if it would be expensive to implement across the whole population.

Evidence on cost-effectiveness related to the key clinical issues being addressed in the guideline was sought. The health economist:

- Undertook a systematic review of the published economic literature.

Literature Review

The health economist:

- Critically appraised relevant studies using the economic evaluations checklist as specified in the NICE guidelines manual
- Extracted key information about the studies' methods and results into evidence tables (included in Appendix I)
- Generated summaries of the evidence in NICE economic evidence profiles (included in the relevant chapter for each review question) – see below for details.

NICE Economic Evidence Profiles

The NICE economic evidence profile has been used to summarise cost and cost-effectiveness estimates. The economic evidence profile shows an assessment of applicability and methodological quality for each economic evaluation, with footnotes indicating the reasons for the assessment. These assessments were made by the health economist using the economic evaluation checklist from the NICE guidelines manual. It also shows the incremental costs, incremental effects (for example, quality-adjusted life years [QALYs]) and incremental cost-effectiveness ratio for the base case analysis in the evaluation, as well as information about the assessment of uncertainty in the analysis. See Table 7 of the full version of the guideline for more details.

If a non-UK study was included in the profile, the results were converted into pounds sterling using the appropriate purchasing power parity.

Undertaking New Health Economic Analysis

No new health economic analysis was undertaken for this guideline due to feasibility.

The GDG originally identified the timing of antimicrobial treatment as the highest priority area for original economic modelling. This question was originally intended to determine the cost-effectiveness of early empirical antibiotic use compared to the use of targeted antibiotics following diagnosis. This question changed following agreement of the protocol and examined the timing of empirical antibiotics. The clinical evidence for this question indicates that early empirical antimicrobials (given <1 hour) result in lower mortality than delayed use. The GDG were confident that any resource implications, and therefore costs, would be offset by the benefits in terms of reduced mortality. As a result the GDG agreed that the cost-effectiveness could be deduced without the need to model. Thus, this area was no longer a priority of economic modelling.

An additional lower priority of a pathway approach (the impact of identifying and treating people with sepsis) was also considered. However a pathway approach was considered unfeasible due to the large number of unknowns in the epidemiology of sepsis.

Cost-effectiveness Criteria

NICE's report 'Social value judgements: principles for the development of NICE guidance' sets out the principles that GDGs should consider when judging whether an intervention offers good value for money. In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

- The intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- The intervention costs less than £20,000 per QALY gained compared with the next best strategy

If the GDG recommended an intervention that was estimated to cost more than £20,000 per QALY gained, or did not recommend one that was estimated to cost less than £20,000 per QALY gained, the reasons for this decision are discussed explicitly in the 'Recommendations and link to evidence' section of the relevant chapter, with reference to issues regarding the plausibility of the estimate or to the factors set out in 'Social value judgements: principles for the development of NICE guidance'.

If a study reported the cost per life year gained but not QALYs, the cost per QALY gained was estimated by multiplying by an appropriate utility estimate to aid interpretation. The estimated cost per QALY gained is reported in the economic evidence profile with a footnote detailing the life-years gained and the utility value used. When QALYs or life years gained are not used in the analysis, results are difficult to interpret unless one

strategy dominates the others with respect to every relevant health outcome and cost.

In the Absence of Economic Evidence

When no relevant published studies were found, and a new analysis was not prioritised, the GDG made a qualitative judgement about cost-effectiveness by considering expected differences in resource use between options and relevant UK National Health Service (NHS) unit costs, alongside the results of the clinical review of effectiveness evidence.

The UK NHS costs reported in the guideline are those that were presented to the GDG and were correct at the time recommendations were drafted. They may have changed subsequently before the time of publication. However, the GDG members have no reason to believe they have changed substantially.

Methods Used to Formulate the Recommendations

Expert Consensus

Informal Consensus

Description of Methods Used to Formulate the Recommendations

Note from the National Guideline Clearinghouse (NGC): The guideline was developed by the National Guideline Centre on behalf of the National Institute for Health and Care Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance and related appendices.

Who Developed This Guideline?

A multidisciplinary Guideline Development Group (GDG) comprising health professionals, lay members and researchers developed this guideline.

The group met approximately every 6 weeks during the development of the guideline.

Staff from the National Guideline Centre provided methodological support and guidance for the development process. The team working on the guideline included a project manager, document editor, systematic reviewers (research fellows), health economists and information scientists. They undertook systematic searches of the literature, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the GDG.

Developing Recommendations

Over the course of the guideline development process, the GDG was presented with:

- Evidence tables of the clinical and economic evidence reviewed from the literature. All evidence tables are in Appendices H and I.
- Summaries of clinical and economic evidence and quality (as presented in Chapters 5-16 of the full version of the guideline)
- Forest plots (see Appendix K)

Recommendations were drafted on the basis of the GDG's interpretation of the available evidence, taking into account the balance of benefits, harms and costs between different courses of action. This was either done formally in an economic model, or informally. Firstly, the net benefit over harm (clinical effectiveness) was considered, focusing on the critical outcomes. When this was done informally, the GDG took into account the clinical benefits and harms when one intervention was compared with another. The assessment of net benefit was moderated by the importance placed on the outcomes (the GDG's values and preferences), and the confidence the GDG had in the evidence (evidence quality). Secondly, whether the net benefit justified any differences in costs was assessed.

When clinical and economic evidence was of poor quality, conflicting or absent, the GDG drafted recommendations based on their expert opinion. The considerations for making consensus-based recommendations include the balance between potential harms and benefits, the economic costs compared to the economic benefits, current practices, recommendations made in other relevant guidelines, patient preferences and equality issues. The consensus recommendations were agreed through discussions in the GDG. The GDG also considered whether the uncertainty was sufficient to justify delaying making a recommendation to await further research, taking into account the potential harm of failing to make a clear recommendation.

The GDG considered the 'strength' of recommendations. This takes into account the quality of the evidence but is conceptually different. Some

recommendations are 'strong' in that the GDG believes that the vast majority of healthcare and other professionals and patients would choose a particular intervention if they considered the evidence in the same way that the GDG has. This is generally the case if the benefits clearly outweigh the harms for most people and the intervention is likely to be cost effective. However, there is often a closer balance between benefits and harms, and some patients would not choose an intervention whereas others would. This may happen, for example, if some patients are particularly averse to some side effect and others are not. In these circumstances the recommendation is generally weaker, although it may be possible to make stronger recommendations about specific groups of patients.

The GDG focused on the following factors in agreeing the wording of the recommendations:

- The actions health professionals need to take
- The information readers need to know
- The strength of the recommendation (for example the word 'offer' was used for strong recommendations and 'consider' for weak recommendations)
- The involvement of patients (and their carers if needed) in decisions on treatment and care
- Consistency with NICE's standard advice on recommendations about drugs, waiting times and ineffective interventions (see Section 9.3 in the NICE guidelines manual [see the "Availability of Companion Documents" field])

The main considerations specific to each recommendation are outlined in the 'Recommendations and link to evidence' sections within each chapter of the full version of the guideline.

Rating Scheme for the Strength of the Recommendations

Strength of Recommendations

Some recommendations can be made with more certainty than others. The Guideline Development Group (GDG) makes a recommendation based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. For some interventions, the GDG is confident that, given the information it has looked at, most people would choose the intervention. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the strength of the recommendation).

Interventions That Must (or Must Not) Be Used

The GDG usually uses 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally 'must' (or 'must not') is used if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Interventions That Should (or Should Not) Be Used – a 'Strong' Recommendation

The GDG uses 'offer' (and similar words such as 'refer' or 'advise') when confident that, for the vast majority of people, an intervention will do more good than harm, and be cost effective. The GDG uses similar forms of words (for example, 'Do not offer…') when they are confident that an intervention will not be of benefit for most people.

Interventions That Could Be Used

The GDG uses 'consider' when confident that an intervention will do more good than harm for most people, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the person's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the person.

Cost Analysis

See the relevant chapters in the full version of the guideline (see the "Availability of Companion Documents" field) for specific cost-effectiveness considerations for each guideline review question.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Validation Process

This guidance is subject to a 6-week public consultation and feedback as part of the quality assurance and peer review of the document. All comments received from registered stakeholders are responded to in turn and posted on the National Institute for Health and Care Excellence (NICE) Web site.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

Refer to "Evidence statements" sections in the full version of the guideline for discussion of the evidence supporting each recommendation.

Type of Studies

For most intervention reviews in this guideline, parallel randomised controlled trials (RCTs) were included because they are considered the most robust type of study design that could produce an unbiased estimate of the intervention effects. If the Guideline Development Group (GDG) believed RCT data were not appropriate or there was limited evidence from RCTs, well-conducted non-randomised studies were included. Please refer to Appendix C in the full guideline appendices (see the "Availability of Companion Documents" field) for full details on the study design of studies selected for each review question. For example, the review question on escalation of care did not include any RCTs as randomly assigning people with sepsis to either be referred to a senior healthcare professional or remain under the care of staff with less experience would be highly unethical. The same applies to the review question on timing of antimicrobial treatment: randomly assigning people with sepsis to a delayed intervention would be unethical. The reviews on inotropic agents or vasopressors also included observational studies as the GDG agreed that the evidence presented by those studies could help inform recommendations.

For reviews of diagnostic tests, diagnostic RCTs were considered the first line approach, in which patients are randomised to one diagnostic test or another followed by treatment, and patient outcomes are assessed. If no evidence was identified from diagnostic RCTs, diagnostic accuracy was reviewed using prospective and retrospective cohort studies in which the index test(s) and the reference standard test are applied to the same patients in a cross-sectional design. Two-gate study designs (sometimes referred to as case-control) were excluded. These are cross-sectional studies which compare the results of the index test in patients with an already established diagnosis of the target condition, with healthy controls. This study design is unrepresentative of practice and is unlikely to contain the full spectrum of health and disease over which the test would be used. Studies of this design may lead to the selective inclusion of cases with more advanced disease and over estimations of sensitivity. The inclusion of healthy controls is likely to lead to over-estimations of specificity.

For prognostic reviews, RCTs, pooled analysis of patient level data, and retrospective cohort or prospective cohort studies were included. Case-control studies were excluded because of their high risk of recall bias.

Where data from observational studies were included, the GDG decided that the results for each outcome should be presented separately for each study and meta-analysis was not conducted.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Early recognition of sepsis increases the possibility that the patient will receive appropriate and timely treatment and this provides the best chance of reducing morbidity and mortality.

See the "Trade-off between clinical benefits and harms" sections in the full version of the guideline (see the "Availability of Companion Documents" field) for additional discussion of benefits of specific interventions.

Potential Harms

- The main harm that may come to patients is both lack of identification of suspected sepsis and over diagnosis of suspected sepsis. The first group of patients may not get appropriate treatment. The latter group will be subject to investigations and treatments they might not need, including the use of broad spectrum antimicrobials increasing the risk of antimicrobial resistance at personal or population level if large numbers are over treated in this way.
- The likely benefit of acute hospital care outweighs any potential harm from transfer to hospital. Inappropriate referral to acute hospital services for people at low risk and who can be managed in the community may lead to iatrogenic harm.
- People with sepsis can be difficult to identify. Simple blood tests that would identify people with sepsis and/or people at risk of poor outcomes would be helpful in identifying those who require interventions rapidly. A test which performs poorly will give false reassurance and be of potential harm. The evidence indicated that commonly available blood tests had poor performance overall for diagnosis.
- The Guideline Development Group (GDG) agreed that a dose of empiric antibiotic is unlikely to cause harm to an individual patient except where a patient has an allergy which is severe enough to cause an anaphylactic reaction.
- Oxygen treatment is known not to improve subjective feelings of breathlessness and can be harmful if people are at risk of hypercapnia such as people with chronic obstructive pulmonary disease (COPD) as it may precipitate respiratory failure.

See the "Trade-off between clinical benefits and harms" sections in the full version of the guideline (see the "Availability of Companion Documents" field) for additional discussion of potential harms of specific interventions.

Contraindications

Contraindications

Do not perform a lumbar puncture without consultant instruction if any of the following contraindications are present:

- Signs suggesting raised intracranial pressure or reduced or fluctuating level of consciousness (Glasgow Coma Scale score less than 9 or a drop of 3 points or more)
- Relative bradycardia and hypertension
- Focal neurological signs
- Abnormal posture or posturing
- Unequal, dilated or poorly responsive pupils
- Papilloedema
- Abnormal 'doll's eye' movements
- Shock
- Extensive or spreading purpura
- After convulsions until stabilised
- Coagulation abnormalities or coagulation results outside the normal range or platelet count below $100x10^9$/litre or receiving anticoagulant therapy
- Local superficial infection at the lumbar puncture site
- Respiratory insufficiency in children

Qualifying Statements

Qualifying Statements

- The recommendations in this guideline represent the view of National Institute for Health and Care Excellence (NICE), arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The application of the recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.
- Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and

their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

- At the time of writing, the terminology around sepsis is changing and new international consensus definitions have been published. Previous terminology included terms SIRS (systematic inflammatory response syndrome), severe sepsis and septic shock but new terminology suggests using terms sepsis and septic shock only.

Implementation of the Guideline

Description of Implementation Strategy

Putting This Guideline into Practice

The National Institute for Health and Care Excellence (NICE) has produced tools and resources to help put this guideline into practice.

Putting recommendations into practice can take time. How long may vary from guideline to guideline, and depends on how much change in practice or services is needed. Implementing change is most effective when aligned with local priorities.

Changes recommended for clinical practice that can be done quickly – like changes in prescribing practice – should be shared quickly. This is because health professionals should use guidelines to guide their work – as is required by professional regulating bodies such as the General Medical and Nursing and Midwifery Councils.

Changes should be implemented as soon as possible, unless there is a good reason for not doing so (for example, if it would be better value for money if a package of recommendations were all implemented at once).

Different organisations may need different approaches to implementation, depending upon their size and function. Sometimes individual practitioners may be able to respond to recommendations to improve their practice more quickly than large organisations.

Here are some pointers to help organisations put NICE guidelines into practice:

1. Raise awareness through routine communication channels, such as email or newsletters, regular meetings, internal staff briefings and other communications with all relevant partner organisations. Identify things staff can include in their own practice straight away.
2. Identify a lead with an interest in the topic to champion the guideline and motivate others to support its use and make service changes, and to find out any significant issues locally.
3. Carry out a baseline assessment against the recommendations to find out whether there are gaps in current service provision.
4. Think about what data you need to measure improvement and plan how you will collect it. You may want to work with other health and social care organisations and specialist groups to compare current practice with the recommendations. This may also help identify local issues that will slow or prevent implementation.
5. Develop an action plan, with the steps needed to put the guideline into practice, and make sure it is ready as soon as possible. Big, complex changes may take longer to implement, but some may be quick and easy to do. An action plan will help in both cases.
6. For very big changes include milestones and a business case, which will set out additional costs, savings and possible areas for disinvestment. A small project group could develop the action plan. The group might include the guideline champion, a senior organisational sponsor, staff involved in the associated services, finance and information professionals.
7. Implement the action plan with oversight from the lead and the project group. Big projects may also need project management support.
8. Review and monitor how well the guideline is being implemented through the project group. Share progress with those involved in making improvements, as well as relevant boards and local partners.

NICE provides a comprehensive programme of support and resources to maximise uptake and use of evidence and guidance. See the into practice pages for more information.

Also see Leng G, Moore V, Abraham S, editors (2014) Achieving high quality care – practical experience from NICE. Chichester: Wiley.

Implementation Tools

Clinical Algorithm

Foreign Language Translations

Mobile Device Resources

Patient Resources

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

IOM Domain

Effectiveness

Patient-centeredness

Timeliness

Identifying Information and Availability

Bibliographic Source(s)

National Guideline Centre. Sepsis: recognition, diagnosis and early management. London (UK): National Institute for Health and Care Excellence (NICE); 2016 Jul 13. 50 p. (NICE guideline; no. 51).

Adaptation

Some recommendations were adapted from other National Institute for Health and Care Excellence (NICE) guidelines (as noted in the "Major Recommendations" field).

Date Released

2016 Jul 13

Guideline Developer(s)

National Guideline Centre - National Government Agency [Non-U.S.]

Source(s) of Funding

The National Guideline Centre was commissioned by the National Institute for Health and Care Excellence to undertake the work on this guideline.

Guideline Committee

Guideline Development Group (GDG)

Composition of Group That Authored the Guideline

Guideline Development Group Members: Saul Faust (*Chair*), Professor of Paediatric Immunology & Infectious Diseases & Director, NIHR Wellcome Trust Clinical Research Facility, University of Southampton; Richard Beale, Clinical Director of Perioperative, Critical Care & Pain Services and Consultant in Intensive Care Medicine; John Butler, Consultant in Emergency Medicine & Critical Care Medicine; Enitan Carrol, Chair in Paediatric Infection/Honorary Consultant, University of Liverpool Institute of Infection and Global Health; Simon Nadel, Adjunct Professor of Paediatric Intensive Care; Julian Newell, Corporate Matron, Patient Safety; Jenny O'Donnell, Lay member; Rachel Rowlands, Consultant in Paediatric Emergency Medicine; Mark Simmonds, Consultant in Acute and Critical Care Medicine; Alison Tavare, General Practitioner; Louella Vaughan, Senior Clinical Research Lead, Northwest London CLAHRC; James Wenman, Clinical Development Manager (Paramedic); Catherine White, Lay member

Financial Disclosures/Conflicts of Interest

At the start of the guideline development process all Guideline Development Group (GDG) members declared interests including consultancies, fee-paid work, shareholdings, fellowships and support from the healthcare industry. At all subsequent GDG meetings, members declared arising conflicts of interest.

Members were either required to withdraw completely or for part of the discussion if their declared interest made it appropriate. The details of declared interests and the actions taken are shown in Appendix B in the full guideline appendices (see the "Availability of Companion Documents" field).

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the National Institute for Health and Care Excellence (NICE) Web site . Also available for download in ePub or eBook formats from the NICE Web site .

Availability of Companion Documents

The following are available:

- Sepsis: recognition, diagnosis and early management. Full guideline. London (UK): National Institute for Health and Care Excellence (NICE); 2016 Jul. 583 p. (NICE guideline; no. 51). Available from the National Institute for Health and Care Excellence (NICE) Web site .
- Sepsis: recognition, diagnosis and early management. Appendices. London (UK): National Institute for Health and Care Excellence (NICE); 2016 Jul. (NICE guideline; no. 51). Available from the NICE Web site .
- Sepsis: recognition, diagnosis and early management. Baseline assessment tool. London (UK): National Institute for Health and Care Excellence (NICE); 2016 Jul. (NICE guideline; no. 51). Available from the NICE Web site .
- Sepsis: recognition, diagnosis and early management. Resource impact template. London (UK): National Institute for Health and Care Excellence (NICE); 2016 Jul. (NICE guideline; no. 51). Available from the NICE Web site .

- Sepsis: recognition, diagnosis and early management. Resource impact report. London (UK): National Institute for Health and Care Excellence (NICE); 2016 Jul. 9 p. (NICE guideline; no. 51). Available from the NICE Web site.
- The guidelines manual 2012. London (UK): National Institute for Health and Care Excellence (NICE); 2012 Nov. Available from the NICE Web site.
- Developing NICE guidelines: the manual 2014. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Oct. Available from the NICE Web site.

Patient Resources

The following is available:

- Sepsis: recognition, diagnosis and early management. Information for the public. London (UK): National Institute for Health and Care Excellence (NICE); 2016 Jul. 9 p. Available in English and Welsh from the National Institute for Health and Care Excellence (NICE) Web site. Also available for download in ePub or eBook formats from the NICE Web site.

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